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TITLE: Predictors and Neuropsychiatric Profile of Nucleus Basalis of Meynert Degeneration in Parkinson Disease

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14. ABSTRACT
The long-term goal of this research proposal is to contribute to the development of improved therapies for non-motor symptoms in sporadic Parkinson disease (PD), specifically the neuropsychiatric symptoms of dementia, psychosis, and apathy. This proposal aims to identify predictors of nucleus basalis of Meynert degeneration and will specifically assess whether *MAPT* H1 haplotype and alpha-synclein levels in the cerebrospinal fluid are associated with nucleus basalis of Meynert volume. This proposal also aims to show that the nucleus basalis of Meynert is associated with psychosis and apathy in PD. To complete these aims we have collected genetic samples and clinical data for 94 advanced PD subjects with MRIs. We have downloaded and processed 228 baseline MRIs and 94 4-year MRIs in an early stage PD cohort. Cholinergic nucleus 4 density (Ch4), our proxy measure for NBM volume, has been generated for these MRI scans. In the early-stage PD cohort, we found that reduced baseline Ch4 density, our proxy measure for NBM volume, was associated with increased risk of future psychotic symptoms. This finding supports targeting this region with deep brain stimulation as a potential symptomatic and neuroprotective therapy for psychosis in PD.

15. SUBJECT TERMS
Parkinson disease; Parkinson disease dementia; Dementia; Psychosis; Apathy; Nucleus basalis of Meynert; Basal forebrain; Acetylcholine; Alpha-synuclein; Microtubule associated protein tau (*MAPT*); Deep brain stimulation.

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1. **INTRODUCTION:**

Degeneration of nigrostriatal dopaminergic neurons is the primary cause of motor symptoms in Parkinson disease (PD), and the diagnosis of PD is based on the presence of these symptoms. However, extra-nigral pathology is a significant contributor to PD non-motor symptoms and much of the morbidity of the disease. Degeneration of the nucleus basalis of Meynert (NBM), which provides cholinergic innervation to the entire neocortex, is a feature of PD and PD dementia.[1-5] The resulting cortical cholinergic deficit is a major contributor to dementia in PD.[1, 6-10] Low frequency deep brain stimulation (DBS) of the NBM is currently being considered as a treatment strategy to improve the cholinergic deficit resulting from NBM degeneration. Low frequency DBS may stimulate remaining cholinergic neurons to release cortical acetylcholine and offer neuroprotection via release of growth factors. The **objectives** of this research are 1) to identify <u>molecular markers</u> that predict greater NBM degeneration in <u>sporadic PD</u> and 2) to expand the neuropsychiatric symptom profile associated with NBM degeneration in <u>sporadic PD</u>. This report represents the research completed in the first 12 months of this 2-year award.

2. **KEYWORDS:**

Parkinson disease; Parkinson disease dementia; Dementia; Psychosis; Apathy; Nucleus basalis of Meynert; Basal forebrain; Acetylcholine; Alpha-synuclein; Microtubule associated protein tau (*MAPT*); Deep brain stimulation.

3. **ACCOMPLISHMENTS:**
   A. **What were the major goals of the project?**

   - **Aim 1a** – In an advanced PD cohort of 120 subjects at UVA, determine if PD subjects with MAPT H1/H1 diplotype have reduced NBM volume compared to PD subjects without this genotype.
     - **Goal/Major Task 1:** Recruit advanced PD subjects for DNA sample collection, use of clinical data
       - Milestone Achieved: 50% enrollment for Major Task 1 achieved with 66/120 subjects recruited through end of Q2FY2017.
       - Milestone: Completion of study enrollment and DNA sample collection for 120 subjects total – projected 18 months. At end of Q42017, 94 subjects recruited accounting for 78% completion of recruitment goal.
     - **Goal/Major Task 2:** Generate genotypic data for analysis
       - Milestone: MAPT haplotype generated for 120 subjects – projected 19 months.
     - **Goal/Major Task 3:** Data Analysis
       - Milestone: Submission of abstract to conference – projected 23 months
       - Milestone: Submission of manuscript to journal – projected 24 months

   - **Aim 1b** – In an early-stage PD cohort, determine if PD subjects with the MAPT H1/H1 diplotype have greater reduction in NBM volume over 4 years compared to PD subjects without this genotype.

   - **Aim 2** – In an early-stage PD cohort, determine if elevated CSF alpha-synuclein at baseline is associated with greater reduction in NBM volume over 4 years.
     - **Goal/Major Task 4**: Data Analysis
       - Milestone: Submission of abstract to conference – projected 15 months
       - Milestone: Submission of manuscript to journal – projected 17 months

   - **Aim 3** – In an advanced PD cohort of 70 subjects at UVA, to calculate NBM volumes and compare volumes between those with and without psychosis and apathy.
     - **Goal/Major Task 5:** Enrollment and Clinical Assessments
       - Milestone: 50% of enrollment reached, 35 subjects total – projected 9 months. 14 subjects have been enrolled. This Milestone is 40% completed.

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- Milestone: Completion of Study Enrollment and DNA sample collection for 70 subjects total – projected 21 months
    - **Goal/Major Task 6:** Data Analysis
        - Milestone: Submission of manuscript to journal – project 24 months

B. **What was accomplished under these goals?**
- For Major Task 1, we have recruited and enrolled 94 subjects through the end of Q4FY2017. This exceeds anticipated enrollment of 90 subjects by this time-point. We passed milestone of 50% enrollment ahead of schedule. Clinical data for these enrolled subjects is being entered into a research database. MRIs for this cohort have been downloaded and processed.
- *Major Task 2 and 3 are contingent on completion of Major Task 1.*
- For Major Task 4, baseline MRI scans for 228 PD subjects and 4-year MRI scans for 94 of these PD subjects are available and have been downloaded for analysis. These scans have been processed through imaging quality and voxel-based morphometry pipelines. Values for the cholinergic 4 (Ch4) nucleus, our proxy measure for the NBM, have been generated. The following paragraph describes these methods and was included in a submitted manuscript.
    - Baseline brain magnetic resonance imaging (MRI) sequences were obtained from the PPMI database. Using the MP-RAGE T1 sequence, we applied voxel-based morphometry methodology.[11, 12] Briefly, images were spatially normalized to standard stereotactic space through both an affine and high dimensional non-linear registration. MRI scans were segmented into gray and white matter and high-dimensionally fit to the Montreal Neurological Institute (MNI) standard space using the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat/) in conjunction with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB (Mathworks, Natwick, MA). To improve fidelity of segmentation for low contrast subcortical regions, we utilized Lorio et al.'s enhanced tissue probability map over SPM12's standard tissue priors.[13] Warping of subject images utilized the Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra (DARTEL) algorithm, which is embedded in SPM12. To preserve absolute volume of grey matter, segmented images were multiplied by the relative voxel volumes contained within the Jacobian determinant matrix of the deformation field.[12] Basal forebrain grey matter density was measured according to a probabilistic map of cholinergic nuclei 1, 2, and 3 (Ch123) and Ch4 for the reference MNI single subject brain that was derived from 3D reconstruction of histological sections.[14] Relative Ch4 density was calculated with a custom MATLAB script which multiplied the gray matter density value for each voxel by the weighting contained within the probabilistic map. Weighted gray matter density values were summed bilaterally according to cholinergic cell group (Ch4 or Ch123).[15] See **Figure 1.**
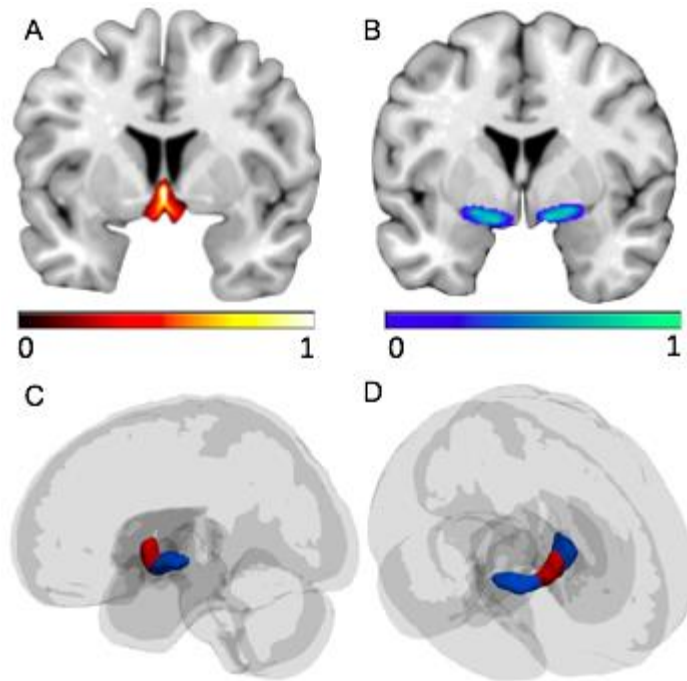
Figure 1. Cholinergic nuclei 1, 2, and 3 (Ch123) (red) and cholinergic nucleus 4 (Ch4) (blue) overlaid on brain anatomy (grey-scale). Coronal slices (A, B) and surface mesh reconstructions (C, D) show the location of the nuclei in Montreal Neurological Institute (MNI) anatomic space. The color scale in A and B indicates the probability (range 0.001 – 1) that a voxel belongs to that cholinergic nucleus.

- For Major Task 5, we have collected data for 14 PD subjects. These subjects have brain MRIs and have completed psychosis and apathy assessments. A protocol amendment allowing prospective collection of additional cohort of PD subjects with brain MRI and psychosis and apathy assessments was approved. Clinical data for these subjects are being systematically collected for entry into research database.
    - We have been slower to recruit for Major Task 5 than anticipated. This is largely a function of a lower rate of PD patients undergoing pre-surgical evaluations compared to the past, what our recruitment estimates were based on. Even instituting a formal process to identify all new potential subjects in a timely way does not address the lack of potential subjects. We have begun to recruit additional PD subjects not undergoing pre-surgical evaluations to supplement recruitment.
- Major Task 6 as written is contingent on completion of Major Task 5. At the same time as our enhanced recruitment efforts for Major Task 5, we analyzed data available in the PPMI cohort to perform part of Aim 3, that is, to compare NBM volumes between those with and without psychosis. The following paragraph describes our results and was included in a submitted manuscript.
    - Cholinergic nuclei densities at baseline were available for 228 PD subjects. In a logistic regression model adjusted for age and sex, Ch4 density was associated with lower risk of reporting psychotic symptoms on 2 or more occasions (OR=0.96 (for an increase in density of 1 unit), p=0.03). Ch4 density at baseline was also available for 101 controls (mean=87.9; SD=9.4). Between healthy controls, PD subjects with 0 or 1 psychotic event, and PD subjects with 2 or more psychotic events, there were no significant differences in age or sex (p>0.05). PD subjects with 2 or more psychotic events had significantly lower baseline Ch4 density compared to healthy controls (p=0.02), but PD subjects with 0 or 1 psychotic events did not (p=0.51). There was no difference in Ch123 density between PD subjects with 2 or more psychotic events and healthy controls (p=0.31). See **Figure 2.** In conclusion, reduced baseline Ch4 density, our proxy measure for NBM volume, is associated with increased risk of future psychotic symptoms.
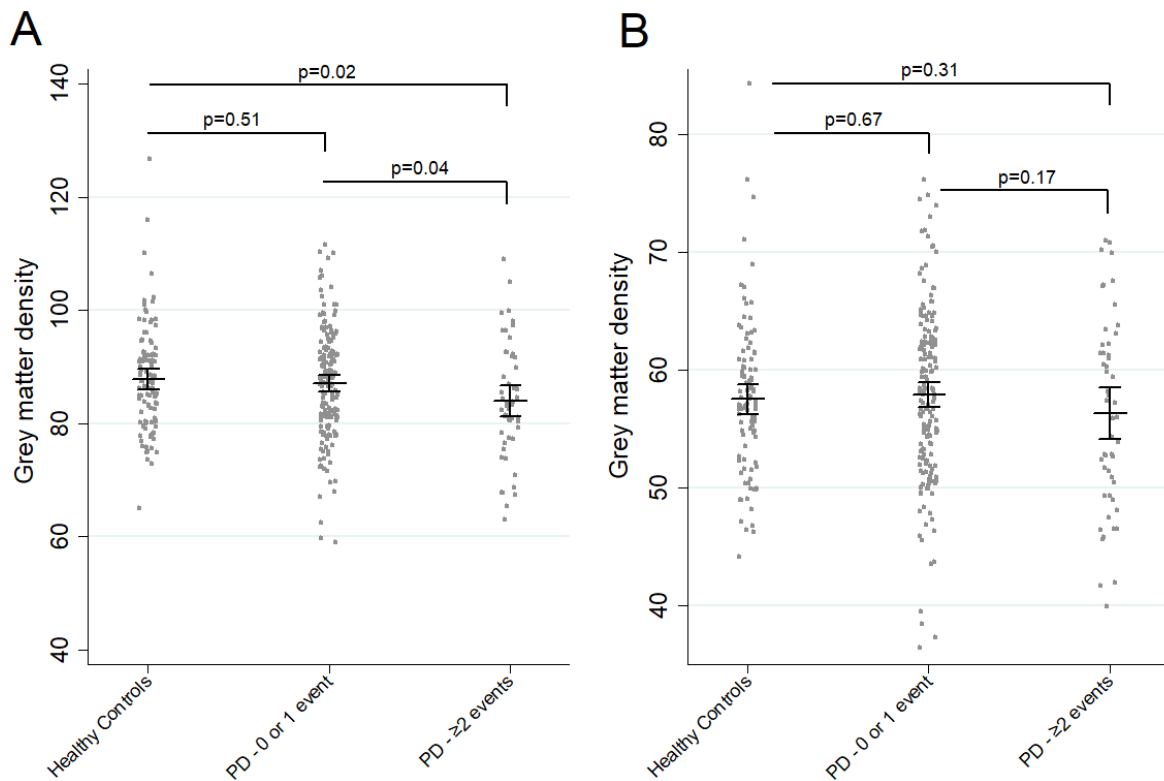
Figure 2. The horizontal lines designate mean values of cholinergic nuclei density for (A) cholinergic nucleus 4 (Ch4) and (B) cholinergic nuclei 1, 2, and 3 (Ch123) in 101 healthy controls, 176 Parkinson disease subjects with 0 or 1 psychotic event, and 52 Parkinson disease subjects with 2 or more psychotic events. Error bars indicate 95% confidence intervals.

C. **What opportunities for training and professional development has the project provided?**
   - The project was not intended to provide training and professional development opportunities but it has provided the following opportunities.
       - Dr. Matthew Barrett, the PI, presented an abstract poster and attended the *Neuroimaging in Parkinson's Disease and Related Disorders Symposium* June 9-10, where he gained insight into current state of neuroimaging research in Parkinson disease from experts in the field.
       - Through his work on this project and under the mentorship of Dr. Jason Druzgal, a co-investigator, Jamie Blair, a neuroscience graduate student, has gained training and greater proficiency in the processing and analysis of structural MRI imaging.

D. **How were the results disseminated to communities of interest?**
   - 2 abstracts resulting from research supported by this grant were presented in the first year of the grant.
       - Barrett, M.J., Smolkin, M.S. Baseline clinical predictors of future psychotic symptoms in de novo Parkinson disease. [poster] International Parkinson and Movement Disorders Society 21st International Congress. 2017 Jun.
       - Barrett, M.J., Sperling, S.A., Pusso, A.N., Blair, J., Druzgal, J. Nucleus basalis of Meynert volume and cognition in Parkinson disease. [poster] Neuroimaging in Parkinson's Disease and Related Disorders Symposium. 2017 Jun.
   - 1 manuscript resulting from research supported by this grant has been submitted for publication.
       - Barrett, M.J., Blair, J.C., Sperling, S.A., Smolkin, M.E., Druzgal, T.J. Baseline symptoms and basal forebrain volume predict future psychosis in early Parkinson disease.

E. **What do you plan to do during the next reporting period to accomplish the goals?**
- For Major Task 1, we will continue to enroll subjects for this study with target enrollment of 15 in Q3. Clinical data for already enrolled subjects and prospectively enrolled subjects will continue to be entered into a clinical research database.
- Following completion of recruitment under Major Task 1, we will complete genotyping and analysis in Major Task 2 and 3.
- For Major Task 4, additional 4-year MRI scans will be added to those already downloaded as they become available. These additional scans will be processed using the imaging quality and voxel-based morphometry pipelines that have already been developed.
- For Major Task 5, we will continue to prospectively identify and enroll subjects who complete psychosis and apathy assessments as part of neuropsychological testing. We will continue to enroll additional subjects to obtain brain MRIs for research to expand this cohort.
- For Major Task 6, we will analyze data from Major Task 5 when complete. We expect that the manuscript evaluating the relationship between Ch4 density, a proxy measure of NBM volume, and psychotic symptoms will be published in the next reporting period. We will pursue analysis of the available advanced PD cohort using alternative measure of apathy to analyze the relationship between Ch4 density and apathy.

4. **IMPACT:**

A. **What was the impact on the development of the principal discipline(s) of the project?**
- In the submitted manuscript described above, we found that reduced cholinergic nucleus 4 (Ch4) density at baseline, a proxy for nucleus basalis of Meynert volume, was associated with risk for future psychotic symptoms. This finding supports other work to target this region with deep brain stimulation as a potential symptomatic and neuroprotective therapy. This finding also supports the potential utility of Ch4 density as a neuroimaging biomarker to identify a diffuse malignant subtype of PD and to predict more rapid disease progression. This work could also influence the field of biomarker research in PD. Our data suggest that Ch4 density has the potential to be a valuable neuroimaging biomarker, that is, Ch4 density may be neuroimaging measure of disease severity that could be followed over time, thus serving as a surrogate biomarker in PD.
- Due to continued data collection prior to analysis, the greatest potential impacts of this research have not yet been realized.

B. **What was the impact on other disciplines?**
- Nothing to Report.

C. **What was the impact on technology transfer?**
- Nothing to Report.

D. **What was the impact on society beyond science and technology?**
- Nothing to Report.

5. **CHANGES/PROBLEMS:**

A. **Changes in approach and reasons for change**
- We are pursuing supplemental recruitment and 2 alternative approaches to accomplish Aim 3. The reason for these changes in approach is that our planned recruitment for this Aim (Major Task 5) has been slower than expected. We will continue to recruit subjects for this aim as originally planned and are supplementing this with other approaches to ensure that we perform the comparisons described for this aim.
  - Supplemental Recruitment: We are supplementing recruitment with prospective enrollment of PD subjects with brain MRI for research only. These subjects are

combined with advanced PD subjects undergoing clinical MRI as part of pre-surgical planning.

- Alternative Approach #1: We plan to evaluate whether NBM volume, as measured by Ch4 density is associated with apathy in advanced PD using the The Frontal Systems Behaviour Scale (FrSBe) Apathy subscale as our outcome measure. This measure has been collected in 82 advanced PD subject and allows us to meet and surpass our original recruitment goal of 70.
- Alternative Approach #2: We have addressed the question whether NBM volume, as measured by Ch4 density, is associated with psychotic symptoms using data from the Parkinson's Progression Markers Initiative. We found that lower Ch4 density at baseline was associated with increased risk of future psychotic symptoms. These results have been prepared as a manuscript which has been submitted for publication.

B. **Actual or anticipated problems or delays and actions or plans to resolve them**
   - It is possible that despite recruitment of an additional cohort of research subjects, we will not meet our enrollment goal for Major Task 5 during the period of the grant. We have devised two other alternative approaches if this is the case, Alternative Approach #1 and Alternative Approach #2, described above.

C. **Changes that had a significant impact on expenditures**
   - Pursuing the different approaches has not had a significant impact on planned expenditures.

D. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
   - There have been no significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period.

E. **Significant changes in use or care of human subjects**
   - Nothing to Report.

F. **Significant changes in use or care of vertebrate animals.**
   - Nothing to Report.

G. **Significant changes in use of biohazards and/or select agents**
   - Nothing to Report.

6. **PRODUCTS:**

   A. **Publications, conference papers, and presentations**

      - **Journal publications.**
         - Barrett, M.J.*, Blair, J.C., Sperling, S.A., Smolkin, M.E., Druzgal, T.J. Baseline symptoms and basal forebrain volume predict future psychosis in early Parkinson disease. (submitted, under review); acknowledgement of federal support – yes.

      - **Books or other non-periodical, one-time publications.**
         - Nothing to Report.

      - **Other publications, conference papers, and presentations.**
         - Barrett, M.J., Smolkin, M.S. Baseline clinical predictors of future psychotic symptoms in de novo Parkinson disease. [poster] International Parkinson and Movement Disorders Society 21st International Congress. 2017 Jun; acknowledgement of federal support – yes.
         - Barrett, M.J., Sperling, S.A., Pusso, A.N., Blair, J., Druzgal, J. Nucleus basalis of Meynert volume and cognition in Parkinson disease. [poster] Neuroimaging in

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Parkinson's Disease and Related Disorders Symposium. 2017 Jun; acknowledgement of federal support – yes.

B. **Website(s) or other Internet site(s)**
- Nothing to report.

C. **Technologies or techniques**
- Nothing to report.

D. **Inventions, patent applications, and/or licenses**
- Nothing to report.

E. **Other Products**
- This project has allowed development of a biospecimen bank of blood samples from which DNA will be extracted for 94 PD subjects. Clinical data for these individuals, specifically neuropsychological test scores, neuropsychiatric assessments, and clinical characteristics are now stored in databases. Lastly, MR imaging studies have been organized, undergone quality control procedures, and used to generate Ch4 densities for 132 subjects with advanced PD and 228 PD subjects from PPMI.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

A. **What individuals have worked on the project?**

Name:	Matthew Barrett
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0003-4480-0221
Nearest person month worked:	4
Contribution to Project:	Project Organization, Subject Recruitment, Clinical Data Collection, Data analysis
Funding Support:	Commonwealth of Virginia's Alzheimer's and Related Diseases Research Award Fund; (NIH) NeuroNext Network and Azevan Pharmaceuticals, Inc.

Name:	Jason Druzgal
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-7240-9487
Nearest person month worked:	1
Contribution to Project:	MRI Imaging Acquisition, Processing, and Analysis
Funding Support:	Commonwealth of Virginia's Alzheimer's and Related Diseases Research Award Fund; UVA Health System Research Award

Name:	Joseph Flanigan
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Subject Recruitment, Clinical Data Collection
Funding Support:	American Parkinson Disease Association Center for Advanced Research at the University of Virginia

Name:	Jamie C. Blair
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	5
Contribution to Project:	MRI Imaging Acquisition, Processing, and Analysis
Funding Support:	Commonwealth of Virginia's Alzheimer's and Related Diseases Research Award Fund; UVA Presidential Graduate Fellowship

B. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
- Matthew Barrett
  - Nothing to Report.

- Jason Druzgal
  - Nothing to Report.

- Scott Sperling
  - Dr. Sperling is no longer receiving support from Virginia Department of Aging for "A Dementia-Capable Virginia: Expanding No Wrong Door and Implementing NYUCI"
  - He is now receiving 25% salary support from the Virginia Department of Aging for "Enhancing Dementia-Capable Virginia through Novel Service Implementation" from 09/01/2017-08/31/2020.

- Brad Worrall
  - Nothing to Report.

- Jeff Elias:
  - Dr. Elias is no longer receiving support from Insightec Ltd. for "A Pivotal Study to Evaluate the Effectiveness and Safety of ExAblate Transcranial MRgFUS Thalamotomy Treatment of Medication Refractory Essential Tremor Subjects - ET002". He is no longer receiving support from the Focused Ultrasound Foundation, Commonwealth of Virginia, and Heller Foundation for "A feasibility study

investigating the safety and initial effectiveness of transcranial MR-guided focused ultrasound thalamotomy in the treatment of medication-refractory, tremor-dominant Parkinson disease."
- He is receiving 5% salary support as PI of the NIH-funded study "Low Intensity Focused Ultrasound Neuromodulation" from September 2016 – August 2018.

- Mark E Smolkin
  - Mr. Smolkin is now receiving 4% salary support for the NIH-funded study" VentFirst: A Multicenter RCT of assisted ventilation during delayed cord clamping for extremely preterm infants" (PI: Kattwinkel)
  - He is no longer receiving support from NIH U01 for "Melanoma vaccine for helper T cells combined with targeted or immune therapies" (PI: Slingluff). He is no longer receiving support from the NIH P01 "Signaling and Progression in Prostate Cancer" (PI: Paschal).

What other organizations were involved as partners?
- Nothing to Report.

8. **SPECIAL REPORTING REQUIREMENTS**
   A. **COLLABORATIVE AWARDS:** NA
   B. **QUAD CHARTS:** Please see attached.

9. **APPENDICES:**
   A. Quad Chart through Q4Y1.

Predictors and Neuropsychiatric Profile of Nucleus Basalis of Meynert Degeneration in Parkinson Disease

PD150019 Neurotoxin Exposure Treatment Parkinson's Research Program Career Progression Award
W81XWH-16-1-0768

PI: Matthew Barrett, MD MSc   **Org:** Rector and Visitors of the University of Virginia   **Award Amount:** $395,000

Study Aims

• Aim 1 - Determine if PD subjects with MAPT H1/H1 diplotype have reduced NBM volume compared to PD subjects without this genotype.
• Aim 2 - Determine if elevated CSF alpha-synuclein at baseline is associated with greater reduction in NBM volume over 4 years in PD patients.
• Aim 3 - Compare calculate NBM volumes of PD subjects with without psychosis and apathy.

Approach

Aim 1 will be conducted as a cross-sectional cohort study in advanced PD and as a longitudinal cohort study in early-stage PD. Aim 2 will be a longitudinal cohort study in early-stage PD. Statistical methods for Aim 1 and 2 include use of linear regression models to adjust for age, sex, and other significant covariates. Aim 3 is a cross-sectional controlled cohort study in which we will use logistic regression models to adjust for age, sex, and other significant covariates.
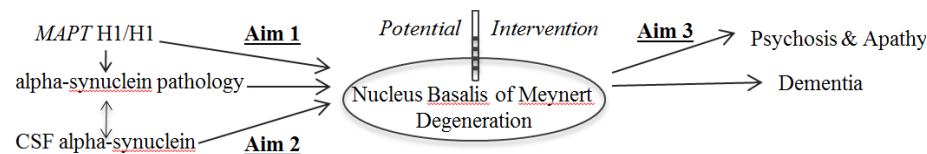
Timeline and Cost

Activities FY	2017	2018
Major Task 1 → Major Task 2		
Major Task 4		
Major Task 5		
Major Tasks 3 and 6		
Estimated Budget ($K)	**$197.5**	**$197.5**

Updated: October 19, 2017

Goals/Milestones

FY2017 Goals – Research subject recruitment and enrollment
☐ **COMPLETED:** 50% Enrollment of subjects for Major Task 1
FY2018 Goals – Completion of enrollment, Genotyping, Data Analysis and Dissemination
☐ Completion of enrollment for Major Task 1
☐ 50% Enrollment of subjects for Major Task 5
☐ Completion of enrollment for Major Task 5
☐ Genotyping of DNA samples
☐ Presentation of results as abstracts and manuscripts.

Comments/Challenges/Issues/Concerns

• Enrollment for Major Task 1 ahead of target. Enrollment for Major Task 5 currently under target. Protocol amended to allow enrollment of additional research subjects and additional approaches are being pursued to address Aim 3.

Budget Expenditure to Date

Projected Expenditure: $197,500
Actual Expenditure: $178,632.59